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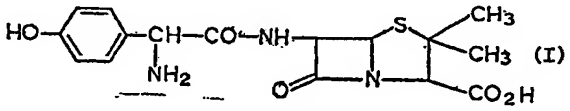
(19)

(54) PENICILLIN SYNTHESIS

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of α-amino(*p*-hydroxybenzyl)penicillin and salts thereof, compounds which were originally disclosed and claimed in Patent No. 978,178.

The present invention provides a process for the production of compounds of the formula (I):



(I)

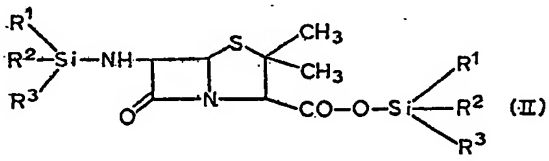
and salts thereof; said process comprising the reaction of a silylated derivative of 6-aminopenicillanic acid with a reactive derivative of of α-amino-*p*-hydroxyphenylacetic acid in which the amino group is protected, and thereafter removing the silyl group(s) by hydrolysis or alcoholysis.

The α-amino-*p*-hydroxyphenylacetic acid may be of either optically active form or a mixture of both optically active forms.

By a silylated derivative of 6-aminopenicillanic acid is meant the product of the reaction between 6-aminopenicillanic acid [6-APA] or a salt thereof and a halotrialkylsilane, dihalodialkylsilane, halotrialkoxysilane, dihalodialkoxysilane or corresponding aryl or aralkyl silanes.

Suitable silylated derivatives of 6-APA include the reaction products of substantially equimolar quantities of 6-APA and a dihalodialkylsilane or the reaction products of one mole of 6-APA and two moles of a halotrialkylsilane.

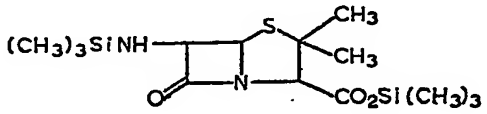
A preferred silylated derivative of 6-APA is that of formula (II):



(II)

wherein R^1, R^2 and R^3 are each alkyl groups of 1—6 carbon atoms, benzyl or aryl groups such as the methyl, ethyl, benzyl or phenyl groups, the methyl group being especially preferred.

Thus in a preferred aspect, the invention provides a process for the production of a compound of formula (I) or salts thereof, which process comprises the reaction of a compound of the formula

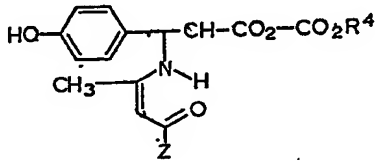


with a reactive derivative of α-amino-*p*-hydroxyphenylacetic acid.

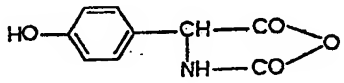
Examples of reactive derivatives include activated esters, acid chlorides or bromides, acid anhydrides or derivatives obtained from a carboxylic acid and a carbodimide or N,N¹-carbonyldi-imidazole.

The amine group of the α-amino-hydroxyphenylacetic acid is protected (i.e. is prevented from taking part in the reaction), for example, by being protonated, included in a cyclic anhydride, condensed with an aldehyde to form a Schiffs base or condensed with an acetoacetate or acetoacetanilide to give an enamine, or by any other method generally used in peptide chemistry.

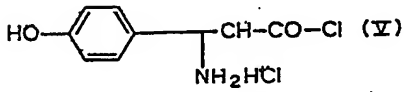
Preferred derivatives of the α-amino-hydroxyphenylacetic acid for this reaction include compounds of general formulae (III wherein R^4 is a alkyl group of 1—6 carbon atoms and Z is an alkoxy group of 1—6 carbon atoms, a NH Ph, NH substituted-Ph, morpholino or dialkylamino group), (IV) and (V):



(III)

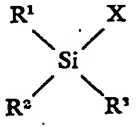


(IV)



The general reaction conditions for the preparation of compounds of general formula (I) are described in our Patent No. 959,853.

The silyl derivatives of 6-aminopenicillanic acid of type (II) used as starting materials in the process of the present invention may be prepared by reacting 6-aminopenicillanic acid or a salt thereof with a compound of the general formula (VI):

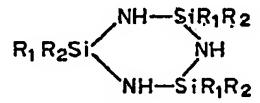


(VI)

in which R^1, R^2 and R^3 are as previously defined and X is any group readily displaced by a nucleophilic reaction involving a carboxylic acid or its salt or an amino group. A preferred X is halogen or $NHSiR_1R_2R_3$.

Examples of general methods of preparation of compounds of general formula (II) in which R^1, R^2 and R^3 are alkyl are described in our British Patent No. 959,853 and

U.S. Patent No. 3,478,018. The other silyl derivatives of 6APA were prepared similarly using the appropriate halosilane (e.g. Me_2SiCl_2, $(MeO)_2SiCl_2$ etc.) or silagene

e.g. 

The following Examples serve to illustrate the invention.

EXAMPLE 1

D-α-Amino-p-hydroxybenzylpenicillin

Dry 6-aminopenicillanic acid (4.32g., 20 m.moles) was suspended in methylene chloride (50 ml.) and trimethylchlorosilane (3.12 ml., 40 m.moles) added. To the stirred mixture triethylamine (5.58 ml., 40 m.moles) was added dropwise and the resulting suspension heated under reflux for 2 hours protected from atmospheric moisture, then cooled and stirred in an ice/water bath. To this was added a solution of the mixed ethoxyformic anhydride of D-α-[(1-methoxycarbonylpropen-2-yl)amino]-p-hydroxy-phenylacetic acid in one portion and the mixture stirred for 1 hour in the cold. [The mixed ethoxyformic anhydride was prepared by stirring for 0.75 hr. at −10° a mixture of ethyl chloroformate (2.0 ml., 21 m.moles), N-methyl-morpholine (0.03g.) and sodium D-α-[(1-methoxycarbonyl-propen-2-yl)amino]-p-hydroxyphenyl acetate (5.75 g., 20 m.moles) in dry acetone (50 ml.)].

The solvents were then distilled at reduced pressure and the residual yellow-brown gum dissolved in a mixture of water (40 ml.) and 4-methylpentan-2-one (40 ml.). The solution was cooled in an ice/water bath and adjusted to pH 1.0 by the dropwise addition of 11.7N hydrochloric acid with rapid stirring. After 0.75 hr. stirring in the cold, the organic layer was separated and rejected. The aqueous layer was washed with fresh 4-methylpentan-2-one (20 ml.) and blown free of solvent with air. The pH of the solution was adjusted to 4.7 with 40% sodium hydroxide when on seeding and cooling the product crystallised. After storage for several hours at 0°, the precipitate was collected by filtration, washed with a little water and dried in air at 40° to give 3.60 g. of the crystalline trihydrate of D-α-amino-p-hydroxybenzylpenicillin (43%, purity 80%). Its identity was confirmed by i.e. spectroscopy and chromatography against an authentic sample.

EXAMPLE 2

D-α-Amino-p-hydroxybenzylpenicillin

D-α-Amino-p-hydroxyphenylacetic acid (8.4g., 50 m.moles) was suspended in acetyl chloride (100 ml.) and finely ground phosphorus pentachloride (20.8g., 100 m.moles) added. The mixture was stirred at 5° for 8 hours with a slow passage of gaseous hydrogen chloride through the mixture, when a yellow gum was formed. Nitrogen was bubbled through the mixture for 2 hours at 5° and the gum hardened and was broken down to a powder by the stirrer. It was collected by filtration and thoroughly washed with dry ether, care being taken to exclude atmospheric moisture. The yellow solid was dried *in vacuo* over potassium hydroxide pellets for several hours to yield 7.2g. (65%) D-α-amino-p-hydroxyphenylacetyl chloride hydrochloride. The I.R. spectrum showed a strong band at 1870 cms.$^{-1}$ which was ascribed to the stretching vibration of the carbonyl group.

The trimethylsilylester of 6-(trimethylsilylamino) penicillanic acid (7.21g., 20m.moles), prepared as in Example 1 with the methylene chloride removed by distillation was dissolved in dry tetrahydrofuran, a freshly distilled sample of quinoline (2.40 ml., 2.60g., 20 m.moles) added, and the solution cooled to 5°C. D-α-Amino-p-hydroxyphenylacetyl chloride hydrochloride (4.44g., 20 m.moles) was added in portions to the stirred solution over 10 minutes. The orange solution was stirred at 5° for a further 20 minutes and then at room temperature for 30 minutes, with exclusion of atmospheric moisture. Water (200 ml.), and a saturated solution of sodium bicarbonate (60 ml) were added with stirring, and then the solution was washed with ether (2×200 ml.), and the ether discarded. The resulting aqueous solution was clarified by filtration, and on examination by paper chromatography showed the presence of D-α-amino-p-hydroxybenzylpenicillin.

EXAMPLE 3

D-α-Amino-p-hydroxybenzylpenicillin

D-α-Amino-p-hydroxyphenylacetic acid (3.34g., 20 m.moles) was suspended in dry dioxan (100 ml.), phosgene was bubbled through the stirred mixture, and the

temperature rose to 40°. When the temperature began to fall again, heating was applied to maintain a temperature of 45° for 4 hours. The resulting yellow solution was cooled and the solvent distilled at reduced pressure to give a light brown oil. Ethyl acetate (15 ml.) and a little decolourising charcoal were added and the mixture stirred for 10 minutes. The yellow solution was clarified by filtration and the filtrate stirred during the addition of 40—60° petroleum ether (200 ml.), when 4-(*p*-hydroxyphenyl) oxazolid-2,5-dione precipitated as a granular solid, yield 3.54g. (92%). Its I.R. spectrum showed strong bands at 3250 cms.$^{-1}$ (NH stretching), 1840, 1770 and 1240 cms.$^{-1}$ (CO stretching).

Dry 6-Aminopenicillanic acid (3.9g., 18 m.moles) was added to a mixture of methylene chloride (50 ml.) and triethylamine (5.0 ml., 36 m.moles) and the resulting mixture stirred at room temperature for 10 minutes, protected from atmospheric moisture. Trimethylsilylchloride (4.7 ml., 37 m.moles) was added dropwise over 5 minutes and the resulting suspension heated under reflux for 60 minutes. The mixture was allowed to cool while dry nitrogen was bubbled through the mixture and then the solution was clarified by filtration into a dry flask. The filtrate was distilled at reduced pressure to remove the solvent, and the resulting colourless oil dissolved in dry dimethylformamide (15 ml.). To the solution was added 2,6-lutidine (2.1 ml., 36 m.moles) and the mixture cooled to —40°. The solution was stirred and a solution of 4-(*p*-hydroxyphenyl)oxazolid-2,5-dione (3.5g., 10 m.moles) in dry dimethylformamide (15 ml.) added over 15 minutes. The stirring was continued at —40° for 10 minutes, and then the mixture was allowed to warm to room temperature and stirred for 16 hours.

A small sample of the resulting solution examined by chromatography indicated the presence of 1.5g. of the penicillin (20% theoretical yield) and some 6-aminopenicillanic acid.

The cloudy solution was concentrated at low temperature *in vacuo* and the residual brown gum dissolved in a mixture of water (50 ml.) and ether (50 ml.), the solution clarified by filtration, and the other separated and rejected. The aqueous solution was adjusted to pH 4.6 by the addition of 2N sodium hydroxide solution, and diluted with water (100 ml.). After stirring the resulting suspension for 60 minutes at 40°, the precipitate was collected by filtration, washed with water (20 ml.) and air-dried at 40° to give 2.3g. of an off-white solid. Comparison of its i.r. spectrum and biochromatogram with an authentic sample showed it to be D-α-amino-*p*-hydroxybenzylpenicillin. Hydroxylamine assay indicated a purity of 16%.

EXAMPLE 4

D-α-Amino-p-hydroxybenzylpenicillin

A solution of the trimethylsilylester of 6-trimethylsilylaminopenicillanic acid prepared as in Example 1 was evaporated to dryness and redissolved in acetonitrile (25 ml.) at —10°. To this was added a solution of the mixed ethoxyformic anhydride of D - α - [(1 - methoxycarbonylpropen - 2 - yl)amino] - *p* - hydroxyphenylacetic acid prepared in acetonitrile (53 ml.) similarly to Example 1. The mixture was stirred in the cold for 30 minutes and at room temperature for a further 30 minutes. Water (50 ml.) and 2N sodium hydroxide (10 ml., 20 m.moles) were added and the resulting solution stirred for 5 minutes.

The acetonitrile was removed by distillation at reduced pressure and to the aqueous concentrate was added 4-methylpentan-2-one (50 ml.). The mixture was cooled in an ice/water bath, acidified to pH 1.0 and the penicillin isolated as described in Example 1. This gave 3.10g. of the crystalline trihydrate of D-α-amino-*p*-hydroxybenzylpenicillin (37%, purity 93%).

EXAMPLE 5

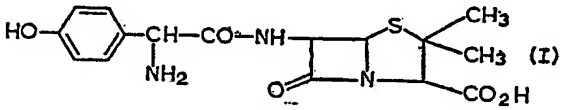
In an apparatus protected from atmospheric moisture dry 6-aminopenicillanic acid (4.32 g., 20 m.moles) was suspended in methylene chloride (42 ml.), cooled (ice/water bath) while protected from atmospheric moisture and triethylamine (5.58 ml., 40 m.moles) followed by dimethyldichlorosilane (2.50 ml., 20.7 m.moles) added. The mixture was heated to reflux for 2 hours and then cooled in an ice/water bath. To it was added a solution of the mixed ethoxyformic anhydride of D-α-[(1-methoxycarbonylpropen-2-yl)amino]-*p*-hydroxyphenylacetic acid in dry acetone, prepared as in Example 1, and the mixture stirred for 30 minutes in the cold and a further 30 minutes at room temperature.

After recooling the stirred solution (ice/water bath) a mixture of water (40 ml.) and 2N sodium hydroxide (10 ml., 20 m.moles) was added and stirring continued for 5 minutes. The organic solvents were then distilled at reduced pressure and 4-methylpentan-2-one (40 ml.) added to the aqueous concentrate. The mixture was cooled in an

ice/water bath and adjusted to pH 1.0 by the dropwise addition of 11.7N hydrochloric acid with rapid stirring. After 45 minutes stirring in the cold, the organic layer was separated and rejected. The aqueous layer was washed with fresh 4-methylpentan-2-one (20 ml.) and blown free of solvent with air. The pH of the solution was adjusted to 4.7 with 2N sodium hydroxide, but, on storage at 0°, the penicillin failed to crystallise. Examination of the solution by biochromatography showed the presence of D-α-amino-*p*-hydroxybenzylpenicillin.

WHAT WE CLAIM IS:—

1. A process for the production of compounds of the formula (I):



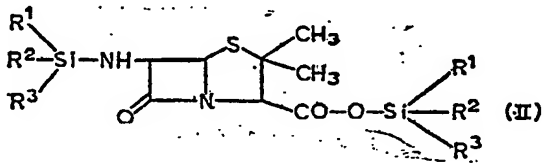
(I)

and salt thereof; said process comprising the reaction of a silylated derivative of 6-aminopenicillanic acid with a reactive derivative of α-amino-*p*-hydroxyphenylacetic acid in which the amino group is protected, and thereafter removing the silyl group(s) by hydrolysis or alcoholysis.

2. A process as in claim 1 wherein the silylated derivative of 6-aminopenicillanic acid is the product of the reaction between 6-aminopenicillanic acid [6-APA] or a salt thereof and a halotrialkylsilane, dihalodialkylsilane, halotrialkoxysilane, dihalodialkoxysilane or corresponding aryl or aralkyl silanes.

3. A process as in claim 2 wherein the silylated derivatives are the reaction products of 6-APA and a dihalodialkylsilane or the reaction products of one mole of 6-APA and two moles of a halotrialkylsilane.

4. A process as in Claim 3 wherein the silylated derivative of 6-APA is a compound of formula (II):



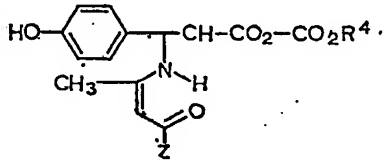
(II)

wherein R^1, R^2 and R^3 are each alkyl of 1—6 carbon atoms, benzyl or aryl groups.

5. A process as in claim 4 wherein R^1, R^2 and R^3 are each methyl groups.

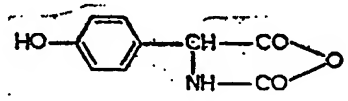
6. A process as in claims 1—5 wherein the reactive derivative of α-amino-*p*-hydroxyphenacetic acid is an activated ester, an acid chloride, bromide or anhydride or the derivative obtained from the acid and a carbodimide or N,N'-carbonyldiimidazole, said reactive derivative having the amino group protected.

7. A process as in claim 6 wherein the reactive derivative is

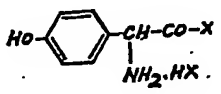


wherein R^4 is a alkyl group of 1—6 carbon atoms and Z is a alkoxy group of 1—6 carbon atoms, a NHPh, NH-substituted Ph morpholino or dialkylamino group.

8. A process as in claim 6 wherein the reactive derivative is:



9. A process as in claim 6 wherein the reactive derivative is:



where X is chlorine or bromine.

10. A process for the preparation of compounds of the formula (I) substantially as described in the Examples herein.

11. A penicillin of formula (I) when prepared by a process of claims 1—10.

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